

REMARKS

Claims 1, 4-12, 15, 17-25, 31, 35, 38, 41 and 133-141 are pending in the application prior to entry of amendments submitted herewith, with claim 8 being withdrawn from further consideration. Claims 1, 4-7, 9-12, 15, 17-25, 31, 35, 38, 41 and 133-141 have been rejected. By amendment herewith, Claims 1, 15, 17, 19, 20, 22, 24, 25, 31, 133-135, 137 and 140 are being changed, Claims 4-12, 18, 21, 23, 41, 138, 139 and 141 are being cancelled and new Claims 142-148 are being added. None of the amendments introduce new matter, and all of the amendments are made without prejudice to or disclaimer or dedication of any subject matter, and a right is specifically reserved to file one or more continuing applications under 35 U.S.C. § 120 claiming any subject matter disclosed in the application.

It is noted that in Claim 1, the reference to prevention of mucositis has been removed from the claim, because, as is clear from the specification at page 3, lines 29-3, treatment of mucositis, as used in Claim 1, means effective to prevent or reduce the incidence, severity and/or duration of the disease, and reference to prevention in Claim 1 has been removed as being redundant.

Rejection under 35 U.S.C. § 112, second paragraph

Claim 20 was rejected under 35 U.S.C. § 112, second paragraph for indefiniteness based on an assertion that "Claims 1 and 20 contradict each other" in relation to stated viscosity properties. The rejection is traversed.

Claim 1, the independent claim, requires that the therapeutic composition exhibits reverse-thermal viscosity behavior over at least some range of temperatures between 1°C and 37°C. Claim 20 requires that amount of the water, as formulated in the composition, does not interact with the poloxamer 407 to impart reverse-thermal gelation properties to the composition.

These limitations of Claim 1 and Claim 20 are not inconsistent, because as discussed in the specification at page 11, line 15 through page 12, line 8, reverse-thermal gelation is a subset of reverse-thermal viscosity behavior, and a composition can exhibit reverse-thermal viscosity behavior without undergoing reverse-thermal gelation.

The rejection under 35 U.S.C. § 112, second paragraph should be withdrawn.

Rejections Under 35 U.S.C. § 102(e) and 103(a) Based On Dobrozsi et al.

Claims 1, 4-7, 9-12, 15, 17-18, 21-23, 31, 35, 38, 41 and 133-136 were rejected under 35 U.S.C. § 102(e) based on an assertion of anticipation by Dobrozsi et al. (US 6,503,955); and Claims 24-25, 133-135 and 137-141 were rejected under 35 U.S.C. § 103(a) based on an assertion of unpatentability over Dobrozsi et al. The rejections are traversed.

For a prior art reference to anticipate the subject matter of a claim under 35 U.S.C. § 102, each and every element as set forth in the claim must be found, either expressly or inherently, described in that single reference. *Verdegaal Bros. v. Union Oil Co. of Calif.*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051 (Fed. Cir. 1987). Also, the elements must be found in the single prior art reference in the particular arrangement of the claim. *Lindemann Maschinenfabrik GMBH v. American Hoist and Derrick Co.*, 730 F.2d 1452, 1458, 221 U.S.P.Q. 481 (Fed. Cir. 1984). Dobrozsi et al. do not disclose each and every element of the rejected claims, expressly or inherently, in the particular arrangement of the rejected claims.

Independent Claim 1 is directed to a therapeutic composition useful for treatment of mucositis as a side effect of cancer therapy, and the composition requires N-acetylcysteine (NAC) in an amount effective as formulated in the composition to provide therapeutic effect for treatment of mucositis; poloxamer 407; and a carrier liquid comprising water in an amount sufficient to interact with the poloxamer 407 to impart reverse-thermal viscosity behavior to the therapeutic composition, and wherein the composition exhibits the reverse-thermal viscosity behavior over at least some range of temperatures between 1°C and 37°C.

Dobrozsi et al. disclose poloxamer 407, NAC, and a reverse-thermal gelation property of some compositions of poloxamer 407 and water, but not in the arrangement, or combination, of Claim 1.

Dobrozsi et al. do not disclose a composition containing NAC in an amount effective as formulated in the composition to provide therapeutic effect for prevention or treatment of mucositis, as is required in Claim 1. Reference is made to the Rule 132 Declaration of Janice M. Troha (the Troha Declaration), and the section of that declaration beginning on page 3 discussing

Dobrozsi et al. As more particularly discussed in the Troha Declaration, Dobrozsi et al. describe their invention as directed to pourable liquid vehicles used to deliver compositions, materials and substances to moistened surfaces and aqueous environments, and the pourable liquid vehicle is such that as the vehicle acquires moisture during use, the vehicle transforms from a liquid to a gel-like form. In a long listing of possible substances that could be delivered using the pourable liquid vehicle, Dobrozsi et al. mention as one possibility “Expectorants/Mucolytics” including, among other things, NAC. Dobrozsi et al. do not disclose any concentrations of NAC for delivery with the pourable liquid vehicle even for the disclosed use of NAC as an expectorant/mucolytic, let alone for the very different use of NAC for treatment of mucositis.

Dobrozsi et al. do not disclose a composition comprising poloxamer 407 and a carrier liquid comprising water in an amount sufficient as formulated in the composition to interact with the poloxamer 407 to impart the reverse-thermal viscosity behavior required by Claim 1. The Examiner’s position with respect to reverse-thermal viscosity appears to rely on that property being inherently present in the pourable liquid vehicle of Dobrozsi et al., because it is clear that that property is not expressly disclosed by Dobrozsi et al. as being present in their pourable liquid vehicle. On the contrary, in a background discussion, Dobrozsi et al. note that water and poloxamer 407 can be combined to form reverse-thermal gelling compositions, but Dobrozsi et al. teach away from the use of such reverse-thermal gelling compositions for drug delivery as being “found to be inadequate, however, as the gel structure readily dissolves in aqueous environments”, and the invention of Dobrozsi et al. is directed to avoiding that identified inadequacy. See, Dobrozsi et al. at column 2, lines 18-67.

The pourable liquid vehicle of Dobrozsi et al. includes polyoxyalkylene block copolymer (also referred to by Dobrozsi et al. as poloxamers) in an amount of 26-100% and optionally one or both of glycol (0-70%) and water (0-50%), provided that the components must be selected and formulated to have a certain viscosity value and to have a property of being convertible from a pourable liquid to a gel-like mixture upon mixing with body fluid. See Dobrozsi et al., at column 4, lines 33-37, column 5, lines 34-47 and column 6, lines 6-15. The pourable liquid vehicle of Dobrozsi et al. need not contain any water at all, and need not contain any liquid (water or glycol), but can be comprised 100% of the poloxamer. Considering the a wide variety of

possible compositional combinations disclosed by Dobrozsi et al. for the pourable liquid vehicle, with a variety of poloxamers, and with or without water or glycol, and in wide specified compositional ranges, it may be possible that one or more possible combinations of components within these broad compositional disclosures by Dobrozsi et al. might exhibit reverse-thermal viscosity behavior. But such possibilities are not sufficient to support an assertion of inherency. It is well settled that the allegedly inherent feature must necessarily result, and not just be possible or probable. *Transclean Corp. v. Bridgewood Services, Inc.*, 290 F.3d 1364, 1373, 62 U.S.P.Q.2d 1865 (Fed. Cir. 2002). The mere fact that a certain thing may result is not enough. *Mehl/Biophile International Corp. v. Milgraum*, 192 F.3d 1362, 1365, 52 U.S.P.Q.2d 1303 (Fed. Cir. 1999).

Moreover, a review of Dobrozsi et al. confirms that not all possible compositions within the broad teachings of Dobrozsi et al. would necessarily exhibit reverse-thermal viscosity behavior. As noted above, in the background section of Dobrozsi et al., Dobrozsi et al. specifically disclose reverse-thermal gelling compositions, and state that such compositions “consist of poloxamer 407 at concentrations ranging from about 10% to 35% by weight of the composition in water” (column 2, lines 30-36), which range is considerably smaller than the optional 0-50% range for water disclosed by Dobrozsi et al. for the pourable liquid vehicle of Dobrozsi et al. That not all compositions within the broad teachings of Dobrozsi et al. would necessarily exhibit reverse-thermal viscosity behavior is further confirmed by two other references cited by the Examiner, Stratton et al. (US 5,861,174) and Krezanoski (US 4,188,373).

Stratton et al. recognize reverse-thermal gelling properties of certain mixtures of some poloxamers and water, including some mixtures containing Pluronic® F-127 (a poloxamer 407 polymer), which is also the polymer used by Stratton et al. in all of the specific examples disclosed in that reference, and Stratton et al. specifically state, at column 6, lines 35-40 (emphasis added):

It is known that a gel will not form when the concentration of the polyoxyethylene[sic]-polyoxypropylene block copolymer in water or dilute buffer is outside of the range of about 20 to 30 percent by weight, as shown in Fig 1 [with data for Pluronic® F-127] . . .

Kreznoski discloses a reverse-thermal gelling pharmaceutical vehicle containing a polyoxyethylene-polyoxypropylene block copolymer (of which Pourable liquid F-127 is a possibility) in an amount of from 10% to about 26 % and water in an amount of from about 74% to about 90%. See, Kreznoski at column 2, line 49 through column 3, line 19 and column 5, lines 43-53.

Moreover, Dobrozsi et al. do not disclose any compositions containing NAC, poloxamer 407 and water, let alone containing the reverse-thermal viscosity behavior required of Claim 1. As noted above, Dobrozsi et al do not require the presence of water in the pourable liquid vehicle. Also, Dobrozsi et al. disclose a wide range of possible poloxamers in a general copolymer formula (column 5, line 51 through column 6, line 6), and for the health care area in particular Dobrozsi et al. list "Pluronic F127, P105 and F108" (column 6, lines 33-38). Moreover, Dobrozsi et al. disclose a wide variety of different pharmacologically active agents that might possibly be delivered using the pourable liquid vehicle. This extensive listing of possible pharmacologically active agents extends from column 7 to column 9 of Dobrozsi et al. and contains at least the following 30 different identified categories of pharmaceutical materials: antibacterial substances, antihistamines, antitussives, antiinflammatories, expectorants/mucolytics, mast cell stabilizers, leukotriene antagonists, methylxanthines, antioxidants, steroids, bronchodilators, antivirals, biologics, analgesics, antiarthritics, antiasthma drugs, urinary tract disinfectives, anticoagulants, anticonvulsants, antidepressants, antidiabetics, antineoplastics, antipsychotics, antihypertensives, muscle relaxants, antiprotozoals, antifungal agents, amoebicidal agents, trichomonoacidial agents and spermicidal. Dobrozsi et al. further list what appears to be hundreds of different sub-categories and specific drugs within those broader categories. NAC is only one possibility from this multitude of listed possibilities for a pharmacologically active agent, and Dobrozsi et al. disclose no specific examples of compositions containing NAC.

Based on the disclosure of Dobrozsi et al. one of ordinary skill in the art even considering the use of NAC as an expectorant/mucolytic would have to select a poloxamer, which might or might not be poloxamer 407, and would have to further select whether or not to use a liquid, and

if using a liquid would have to select from between water and glycol and combinations of water and glycol. This selection process of picking and choosing the particular drug, poloxamer and liquid combination that would be required by one of ordinary skill in the art from among a multitude of possibilities is the antithesis of anticipation.

Clearly, Dobrozsi et al. do not anticipate the therapeutic composition recited in Claim 1, or any of the dependent claims, and the rejection under 37 U.S.C. § 102(e) should be withdrawn.

Moreover, none of the pending claims is obvious over Dobrozsi et al. under 35 U.S.C. § 103(a).

The Examiner asserts that it would be obvious to adjust the compositions of the reference to meet the desired characteristics of the claimed composition, such as characteristics of viscosity by adjusting the amount of copolymer, and in support of that proposition the Examiner cites to the case of *In re Aller*, 220 F.2d 454, 205 U.S.P.Q. 233(CCPA 1955). But the obviousness of any modifications to the subject matter of a prior art reference must be viewed from the perspective of one of ordinary skill in the art considering the teachings of the prior art reference, and not based on hindsight analysis using the invention as a guide.

From the above discussion concerning anticipation, it is apparent that one of ordinary skill in the art considering Dobrozsi et al. would recognize the following from the teachings of Dobrozsi et al.:

1. An advantageous drug delivery vehicle is a pourable liquid vehicle with the compositional attributes disclosed by Dobrozsi et al., and formulated to convert from a pourable liquid to a gel-like form due to dilution with bodily fluids;
2. A teaching away from the use of drug delivery compositions with reverse-thermal gelling properties based on a combination of poloxamer and water as being inadequate because the gel structure readily dissolves in aqueous environments, an inadequacy addressed by Dobrozsi et al. with their pourable liquid vehicle with gel formation triggered by dilution with bodily fluids rather than based on temperature changes; and

3. NAC is useful in the pourable liquid vehicle of Dobrozsi et al. as an expectorant/mucolytic.

Based on these recognitions of the teachings of Dobrozsi et al., if one of ordinary skill in the art were to attempt to modify the pourable liquid vehicle of Dobrozsi et al., the modification would be guided by the teachings of Dobrozsi et al. concerning the desirability of triggering gelation by dilution with bodily fluids and the inadequacy of reverse-thermal gelation. Any such modification by one of ordinary skill in the art would, therefore, be away from compositions containing reverse-thermal gelling and toward the dilution triggered gelling of the pourable liquid vehicle of Dobrozsi et al., and it would not, therefore, be obvious for one of ordinary skill in the art to make modifications in the direction of the features of claimed composition, because one of ordinary skill in the art would not have any motivation to modify the composition of Dobrozsi et al. to achieve purposes different from and contrary to the teachings of Dobrozsi et al.

Also, Dobrozsi et al. disclose NAC only for use as an expectorant/mucolytic, and it would not be obvious for one of ordinary skill in the art to select a concentration of NAC in a different type of drug delivery vehicle (reverse-thermal viscosity behavior) for a different purpose (to treat for mucositis as a side effect of cancer therapy). In that regard, the Troha Declaration is referred to in that it would not be expected from the disclosure of Dobrozsi et al. that NAC would be effective for treating mucositis.

Moreover, the case of *Aller* cited by the Examiner is not on point with the situation presented here. The Examiner cites to the case of *In re Aller*, 220 F.2d 454, 105 USPQ 232 (CCPA 1955) for the proposition:

Normally, changes in result effective variables are not patentable where the difference involved is one of degree, not of kind; experimentation to find workable conditions generally involves the application of no more than routine skill in the art.

The situation presented here with respect to the subject matter of the appealed claims in relation to the disclosures of Dobrozsi et al. is significantly different than the factual situation

presented in *Aller*, and the reasoning behind the holding in *Aller* simply is not applicable to this nonanalogous factual situation.

In *Aller*, the invention was a process for making phenol, and the asserted prior art reference disclosed essentially the same process for making the same product (phenol), except that the invention used a somewhat lower temperature and higher concentration of one reactant, sulfuric acid. The subject matter (particular type of process) and the purpose of that subject matter (to make phenol) were the same in the invention and the prior art reference. Although the inventors in *Aller* asserted that the process of their invention resulted in higher yields of the phenol product, the Court noted that the improved results did not appear to be different in kind relative to the prior art and that logically the improvements can flow equally well from changes in degree resulting from routine variation of temperature and acid concentration, and that there was no showing of anything critical about parameters of the process of the invention.

The current situation is significantly different than the factual situation presented in *Aller*. The claimed invention, as recited in Claim 1, is a therapeutic composition that comprises NAC in an amount effective as formulated in the composition to provide therapeutic effect for treatment of mucositis as a side effect of cancer therapy, together with poloxamer 407 and a carrier liquid comprising water in an amount sufficient as formulated in the composition to interact with the poloxamer 407 to impart the recited reverse-thermal viscosity behavior to the therapeutic composition. In contrast, the pourable liquid vehicle of Dobrozsi et al. is focused on the triggering of gelation through dilution with bodily fluids, which is a fundamentally different mechanism than the reverse-thermal viscosity behavior recited in Claim 1, and Dobrozsi et al. disclose no purpose associated with formulating their pourable liquid vehicle with a drug for treatment of mucositis as a side effect of cancer therapy, and it could hardly be considered routine for one of ordinary skill in the art considering the teachings of Dobrozsi et al. to modify the pourable liquid vehicle of Dobrozsi et al. to include a gelling mechanism different than that disclosed as advantageous by Dobrozsi et al. and formulated to treat a condition not even recognized by Dobrozsi et al. Unlike the facts in *Aller*, the therapeutic composition of Claim 1 and the pourable liquid vehicle of *Dobrozsi et al.* are not essentially the same subject matter. Moreover, the purpose of using NAC is not the same, because the NAC in Dobrozsi et al. is

disclosed for use as an expectorant/mucolytic, whereas NAC in the therapeutic composition of Claim 1 is in an amount effective to provide therapeutic effect for treatment of mucositis as a side effect of cancer therapy. The efficacy of the claimed composition for treatment of mucositis as a side effect of cancer therapy is indeed one of kind, and not of degree with respect to the disclosure of Dobrozsi et al.

None of Claim 1 and the dependent Claims are obvious over Dobrozsi et al, and the rejection under 35 U.S.C. § 103(a) should be withdrawn.

Rejection Under 35 U.S.C. § 103(a) Based On Dobrozsi et al. In View Of Stratton et al.

Claims 1, 4, 15, 17-19, 24-25 and 133-139 were rejected under 35 U.S.C. § 103(a) based on an assertion of unpatentability over Dobrozsi et al. in view of Stratton et al. (US 5,861,174). The rejection is traversed.

It is noted that Claim 1, as amended herewith, requires NAC in an amount effective as formulated in the composition to provide therapeutic effect for treatment of mucositis as a side effect of cancer therapy. The requirement of NAC was formerly the subject of dependent Claim 12, which was not rejected based on Dobrozsi et al. in view of Stratton et al., so that rejection is now moot.

The disclosure by Stratton et al. particularly concerns the use of certain reverse-thermal gelling compositions containing poloxamer for delivery of polypeptides in high concentration. NAC is not a polypeptide, and Stratton et al. is not applicable to NAC. Dobrozsi et al. is as discussed above, and concerns a quite different type of drug delivery composition that is in the form of a pourable liquid vehicle in which gelation is triggered by dilution with bodily fluids.

The rejection under 35 U.S.C. § 103(a) based on Dobrozsi et al. in view of Stratton et al. should be withdrawn.

Rejection Under 35 U.S.C. § 103(a) Based On Krezanoski in view of Boggs

Claims 15, 22, 23 and 136-141 were rejected under 35 U.S.C. § 103(a) based on an assertion of unpatentability over Krezanoski (US 4,188,373) in view of Boggs et al. (US 5,358,705). The rejection is traversed.

Kreznoski discloses a reverse-thermal gelling pharmaceutical vehicle used generally as a carrier for a "pharmaceutically active material, i.e., a drug or medicament," and the pharmaceutical vehicle of Kreznoski is made with certain proportions of polyoxyethylene-polyoxypropylene block copolymers and water. See Kreznoski at column 2, line 63 through column 3 line 19 and column 3 line 61 through column 4, line 3. Kreznoski does not disclose NAC, for any purpose.

As more particularly discussed in the Troha Declaration, Boggs et al. is directed to the use of N-acetylated amino acid complexes in oral care compositions for reducing or preventing dental plaque, or gingival or periodontal diseases, of the oral cavity, through reduction in bacterial binding to the tooth surface. However, as discussed in the Troha Declaration, the disclosure of Boggs et al. of the use of NAC for that purpose would not lead to an expectation that NAC would be efficacious for treatment of mucositis occurring as a side effect of cancer therapy, the pathogenesis of which does not appear to be due to the presence of bacteria.

As discussed above with respect to the Dobrozsi et al., Claim 1 requires, in combination with the other elements of the claim, NAC in an amount effective as formulated in the composition to provide therapeutic effect for treatment of mucositis as a side effect of cancer therapy, which is not disclosed by either Kreznoski or Boggs et al.

Claim 1 and the dependent Claims are not obvious over Kreznoski in view of Boggs et al., and the rejection under 35 U.S.C. § 103(a) should be withdrawn.

The Troha Declaration As Further Evidence of Nonobviousness

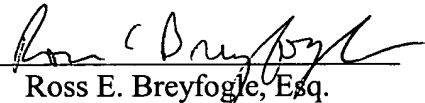
Moreover, reference is made to the Troha Declaration in relation to unexpected properties of the claimed composition for treatment of mucositis, and particularly severe mucositis, occurring as a side effect of cancer therapy. Such efficacy for treatment of mucositis is surprising and unexpected, and further confirms the nonobviousness of the claimed subject matter over Dobrozsi et al., Stratton et al., Kreznoski and Boggs et al., and combinations thereof. The claimed composition is directed toward satisfying a long felt, unmet need for treating mucositis, as discussed in the Troha Declaration, and as recognized by the FDA's designation of a claimed composition for Fast Track status.

It is believed that all of the issues raised in the Office Action have been addressed herein. Should the Examiner maintain any of the rejections of any of the pending claims, it is respectfully requested that it be pointed out with particularity how the cited reference(s) meet each and every term of each claim with respect to which rejection is maintained. In the absence of a persuasive showing to that effect, all pending claims should be allowed.

The application is believed to be in condition for allowance and allowance of all pending claims is earnestly requested. If the Examiner believes that it would be helpful to discuss any of the amendments or remarks presented, or to discuss possible Examiner amendments, the Examiner is respectfully invited to contact the undersigned at the telephone number provided below.

Respectfully submitted,

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